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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/765,086	01/17/2001	Erkki I. Ruoslahti	P-LJ 4575	6131

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EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/765,086	RUOSLAHTI ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,9,13,14,23 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,9,13,14,23 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 8, 9, 13, 14, 23, and 24 are pending and under consideration.

This Office action contains new grounds of rejection.

Claim Rejections - 35 USC § 103, Withdrawn

The rejection of claims 8, 9, 13, 14, 23, and 24 under 35 U.S.C. 103(a) as being unpatentable over WO 99/46284 (IDS, 1999) and Ellerby et al (IDS, September 1999, Nature Medicine 5, 1032-1038) in view of Arap et al (previously cited, 16 January 1998, Science Vol. 279, 377-380) is withdrawn because the declaration filed on 3/12/2004 under 37 CFR 1.131 is sufficient to overcome the Ellerby et al., (1999) reference.

The Following Are New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8, 9, 13, 14, 23, and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This written description rejection is made due to the limitation "antimicrobial peptide having low mammalian cell toxicity when not linked to said prostate-homing peptide" in the base claims 8, 13, and

23. Since the dependent claims 9, 14, and 24 all include this limitation that lacks the written description, these dependent claims are also rejected.

The applicable standard for the written description requirement can be found: MPEP 2163; University of California v. Eli Lilly, 43 USPQ2d 1398 at 1407; PTO Written Description Guidelines; Enzo Biochem Inc. v. Gen-Prove Inc., 63 USPQ2d 1609; and Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

The specification at page 9, first paragraph discloses that antimicrobial peptides, also known as lytic peptides or channel-forming peptides, are broad spectrum anti-bacterial disrupt bacterial cell membranes, causing cell lysis and death. While some antimicrobial peptides such as melittin are not selective and damage normal mammalian cells at the minimum bactericidal concentration, others are selective for bacterial cells. For example, the naturally occurring magainins and cecropins exhibit substantial bactericidal activity at concentrations that are not lethal to normal mammalian cells. Microbial peptide analogs also have been synthesized de novo as described in Javadpour et al., J. Med. Chem. 39:3107-3113 (1996) and others.

However, Javadpour et al., (IDS, 1996) teach at Table 2 at page 9547 and also at the last paragraph of the journal article that only $(KLGKKLG)_3$ behaves similar to magainin or cecropin in terms of discriminating between low toxicity to mammalian cells, all of the rest of the peptide analogs shown in Table 2 have high toxicity to mammalian cells even though the structure is very similar to $(KLGKKLG)_3$.

Thus, the only factor present in the claim is a functional description of the claimed antimicrobial peptides is not seen enough to satisfy written description requirement. There is not even identification of any particular portion of the structure that must be conserved in order to have the recited function. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

It is noted that the instant specification show very good results with a chimeric prostate homing peptide. The specification at Figure 8 has a good data disclosing usefulness of SMSIARL prostate homing peptide because the mice received the chimeric prostate homing pro-apoptotic peptide i.e. pro-apoptotic peptide, $_D(KLAKLAK)_2$, coupled to SMSIARL has the highest survival rate compared to the mice who received either SMSIARL alone or $_D(KLAKLAK)_2$.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that

[he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of antimicrobial peptides with low mammalian toxicity, given that which antimicrobial peptide would have such function. It is the Office' position that the specification does not disclose the structure of a representative of the claimed antimicrobial peptide, or the structure coupled with function; $_D$(KLAKLAK)$_2$ disclosed in the instant specification, the art-known sequences of (KLGKKLG)$_3$, magainin or cecropin is not representative of the genus. Further, $_D$(KLAKLAK)$_2$, (KLGKKLG)$_3$, magainin, and cecropin do not appear to show a common structure in order to meet the function i.e., low mammalian toxicity when not linked to a prostate-homing sequence.

Claims 9, 14, and 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO:207, does not reasonably provide enablement for "a functionally equivalent sequence". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and

8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claims 9, 14, and 24 are interpreted as drawn to method involving a chimeric prostate-homing pro-apoptotic peptide, wherein the prostate-homing peptide is a "functionally equivalent sequence" of SMSIARL (SEQ ID NO: 207).

This rejection is made because of the definition of "functionally equivalent sequence" of SMSIARL (SEQ ID NO: 207) at the specification at page 78, first paragraph, a prostate-homing peptide. The specification define the term "functionally equivalent sequence," as used herein in reference to the sequence SMSIARL (SEQ ID NO: 207), means a sequence that binds selectively to the endothelium of prostatic blood vessels, as shown in FIG. 9 for the sequence SMSIARL (SEQ ID NO: 207), and that functions similarly in that the sequence binds selectively to ***the same receptor***. However, the specification does not teach which receptor SMSIARL (SEQ ID NO: 207) binds to. The specification at Fig. 9 does not disclose any specific receptor so that one in skill art could carry out the assay which receptor applicant is referring to.

Zitzmann et al., (Cancer Res. 2002 Sep 15;62(18):5139-43) is cited to show the state of art. Zitzmann et al., teach that MDA-MB 435 cells express RGD-receptors, α_V integrins, on their surface and the receptor is also up-regulated in angiogenic endothelial cells. Despite this, previous studies, using bacteriophages displaying the RGD-4C-peptide that was fused to a surface protein and that was introduced into the blood stream of mice carrying MDA-MB 435 xenografts, had shown that the RGD-4C-phages attached exclusively to endothelial cells, not to tumor cells. This seemingly

contradictory result may be best explained by the size difference between the peptide displaying bacteriophage and the peptide FITC conjugate. It is known that blood vessels in tumor have an increased vascular leakiness, as compared with vessels of normal tissue, and the RGD-4C-FITC complex may be sufficiently small to penetrate into the tumor tissue through the endothelial vessel lining. The display phages, in contrast, might be too large. Binding of the peptide during sample preparation appears to be an unlikely possibility, because the mice were perfused through the heart, and the major portion of blood and unbound peptide was washed out before removing the tumor and control organs. Zitzmann et al teach the confusion about where phage-screened peptides bind to "because of the unavailability of an informative assay". Since the specification does not teach the assay to see whether a peptide is "functionally equivalent sequence" of SMSIARL (SEQ ID NO: 207), it is concluded that it requires undue experimentation to practice the full scope of the invention.

Considering the unpredictable state of art, limited guidance, no examples in the specification how to assay whether a peptide is "functionally equivalent sequence" of SMSIARL (SEQ ID NO: 207), broad breath of the claims, it is concluded that undue experimentation is required to practice the invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina C Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D.
Examiner
Art Unit 1642